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10/069,385	02/19/2002	Paul Robert Atkinson	X-13268	3249

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EXAMINER	
O HARA, EILEEN B	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 06/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,385	ATKINSON ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/01/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 14-21 are pending in the instant application. Claims 1-13 have been canceled as requested by Applicant in the Preliminary Amendment filed Feb.19, 2002.

All claims are currently under examination.

Priority

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). Priority to provisional application 60/153,433 should be referred to in the first sentence.

Specification

3.0 The disclosure is objected to because of the following informalities.

3.1 There are two tables labeled "Table I", one on page 26 and the second on page 30. The specification should be amended so that the second table is labeled as "Table II" and the subsequent tables labeled appropriately. Additionally, the specification also needs to be amended so that the correct table is referred to.

3.2 On page 5, lines 16-17, SEQ ID NO: 3 is defined as a protein but is a nucleic acid in the sequence listing.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 14-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a FLINT analog that is protease resistant to proteolysis between positions 218-219 of SEQ ID NO: 1 (mature form) or positions 247 and 248 of SEQ ID NO: 3 (full-length or native) and divalent cations, does not reasonably provide enablement for other FLINT analogs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to FLINT analogs. The specification on page 5, lines 9-17 define "FLINT analog" as a protein derivative of mature FLINT (SEQ ID NO: 1) or native FLINT (SEQ ID NO: 2) comprising one or more amino acid deletions, additions, substitutions or inversions of residues within SEQ ID NO: 1 or 2 that comprise FLINT analogs that are resistant to proteolysis between positions 218-219 of SEQ ID NO: 1 or positions 247 and 248 of SEQ ID NO: 2. Therefore, the claims encompass proteins that have no structural limitations, and no functional limitations. A protein with a completely different amino acid sequence would meet the limitations of the claims, as long as it was resistant to proteolysis between the specific amino acid residues recited in the specification.

Specifically, the instant specification does not identify those amino acid residues in the amino acid sequence of SEQ ID NOS: 1 or 2 which are essential for its biological activity and structural integrity and those residues which are either expendable or substitutable. In the absence of this information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis before they could even begin to rationally design a functional FLINT analog protein having other than a natural amino acid sequence with a mutation in the area of amino acids 218-219 or 247-248, or the specific mutations listed on page 5, line 25. The disclosure of a few FLINT analogs that are protease resistant is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass FLINT analogs as defined in the specification.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by

amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

The current claim limitations are analogous to those of claim 7 of U.S. Patent Number 4,703,008 which were held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 U.S.P.Q. 2d, 1016 (CAFC, 3/5/91, see page 1026, section D). In that instance, a claim to a nucleic acid encoding a polypeptide having an amino acid sequence sufficiently duplicative of the amino acid sequence of erythropoietin (EPO) so as to have a specified biological activity was held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement. The disclosure upon which that claim was based described a recombinant DNA encoding EPO and a few analogs thereof. The court held that what is necessary to support claims of this breadth is a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For proteins, that means disclosing how to make and use enough sequences to justify the grant of the claims sought.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These

factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

For the reasons discussed above, due to the large quantity of experimentation necessary to generate the large number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any specific functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

4.2 Claims 14-21 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes the polypeptide sequences consisting of SEQ ID NOS: 1 and 2 and the variants thereof on page 5, which are shown to bind FAS ligand and are protease resistant. However, the claims as written include polypeptides comprising homologues, encompass polypeptides that vary substantially in length and also in amino acid composition. The instant disclosure of a few polypeptides with limited mutations that bind FAS ligand and are protease resistant does not adequately support the scope of the claimed genus, which

encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses,

however, a few polypeptides with specific mutations that are proposed to possess the same activity as SEQ ID NOS: 1 and 2. Protein function, however, cannot be reliably predicted from protein sequence homology. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does not allow predictability in this instance. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences. The instantly claimed genus is not so limited and the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify the polypeptides encompassed.

4.3 Claims 19-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 19-21 encompass pharmaceutical formulations comprising isolated FLINT analogs and divalent cations. Thus the claims encompass a "pharmaceutical use" for the compositions. For the claims to be enabled, the specification must teach how to use the composition for at least one pharmaceutical use without undue experimentation. Steadman's Medical Dictionary (24th Edition, 1982) defines "drug" as "a therapeutic agent; any substance other than food, used in the prevention, diagnosis, alleviation, treatment or cure of disease in man and animal." Ansel et al. (Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Edition), says "A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in humans or in other animals. One of the most astounding qualities of drugs is the diversity of their actions and effects on the body." The following are examples of "pharmaceutical uses": administering vitamin supplements (preventing disease); using labeled antibodies for in vivo imaging (diagnosing disease); administering a substance to alleviate a symptom of a disease (alleviating or treating disease); and administering an antibiotic (curing bacterial infection). Administering a polypeptide to produce antibodies to protect the individual from contracting a disease, i.e., vaccination, is a pharmaceutical use, however, administering a polypeptide to produce antibodies which are then collected from the animal and used in various ways is not a pharmaceutical use.

In the present situation, to enable a pharmaceutical use for the FLINT anlogs, the specification is required to teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment or cure of a disease in the animal to which the substance is administered. However, the specification does not provide adequate guidance as to how the FLINT analog and divalent cation compositions

can be used to treat or diagnose any disorders. The specification on page 3, line 22 to page 4, line 13, states that the FLINT analog-divalent cation complex will have uses including the preparation of pharmaceutical compositions, and use in treatment and/or prevention of disorders that may be associated with the binding of Fas to FasL, and/or LIGHT to the LTβR and/or TR2/HVEM receptors.

However, there are no examples of treatment by administration of the FLINT analog-divalent cation complex, and the specification provides protocols for two hypothetical disorders (Examples 7 and 8). It is not predictable from the in vitro experiments of the instant specification or from the teachings of the prior art that the FLINT polypeptides could be used to treat the diseases or disorders asserted in the specification.

Due to the lack of direction or guidance in the specification, the absence of working examples and teachings of the prior art, the unpredictability in the art, and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use a "pharmaceutical formulation" comprising FLINT analog-divalent cation complex. However, the specification enables the use of "a composition" comprising the comprising FLINT analog-divalent cation complex and a pharmaceutically acceptable carrier. Deletion of the word "pharmaceutical" in claim 19 would therefore obviate the rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 14-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As defined on page 5 of the specification, a "FLINT analog" encompasses proteins that have no structural limitations, and no functional limitations. Therefore, the claims are considered indefinite, since the claims do not clearly set forth the metes and bounds of the patent protection desired.

Prior Art

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Gentz et al., WO 98/30694, July 19, 1998, which discloses a polypeptide comprising 300 amino acids, which is identical to the polypeptide of SEQ ID NO: 1 of the instant invention over the 271 amino acids of SEQ ID NO: 1. Gentz et al. does not anticipate the instant invention, since Gentz did not appreciate that the full length polypeptide of SEQ ID NO: 1 undergoes proteolysis in vivo to produce at least two major peptide fragments (amino acids 1-218 and 219-271).

Conclusion

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-

0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (571) 272-0887.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, se **http://pair-direct.ispto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Eileen B. O'Hara

Patent Examiner